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Serum and urinary high density lipoproteins in glomerular disease with proteinuria

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Serum and urinary high density lipoproteins in glomerular disease with proteinuria. The serum lipoprotein concentrations, including high–density lipoprotein (HDL) subfractions and apolipoproteins A1 and B were measured in 21 patients (14 male and seven female) with nephrotic range proteinuria (>3g/24hr), well maintained renal function (creatinine clearance >35 mliter/min/1.73m^2) and biopsy–proven primary glomerular disease. In these, and in a further five patients (creatinine clearance >15 mliter/min/1.73m^2), urinary apolipoprotein A1 output was determined. Total HDL cholesterol was similar in patients and controls, but in male patients, HDL2 was low (0.54 ± 0.10 mmole/liter, mean ± SEM) compared to controls (0.75 ± 0.04 mmole/liter, $P < 0.05$) and HDL3 was high (0.81 ± 0.07 in patients and 0.63 ± 0.02 mmole/liter in controls, $P < 0.01$). In women, there was a similar tendency for HDL2 to be lower in patients (0.68 ± 0.18 mmole/liter) than in controls (0.85 ± 0.10 mmole/liter). Multiple regression analysis revealed that major determinants of the urinary apolipoprotein A1 output were the urinary protein output and selectivity index (multiple $r = 0.85$). Furthermore, some patients lost apolipoprotein A1 into their urine at rates indicating increased production of apolipoprotein A1 in the nephrotic syndrome. The serum HDL subfraction concentrations in the nephrotic syndrome could be exaplained by a combination of increased HDL production and increased urinary loss of low molecular wt HDL.

The association between lipemic serum and coaguable urine has been recognized for over 150 years [1], and by the early part of this century the occurrence of hypercholesterolemia [2] and hypertriglyceridemia [3] in the nephrotic syndrome (NS) was established. Later, serum lipoproteins were studied in nephrotic patients [4–9]. Changes in serum lipoprotein concentrations are relevant to the controversial issue of whether or not the risk of ischemic heart disease (IHD) in NS is increased [9–12]. With the renewed interest in low levels of serum high density lipoprotein (HDL) as a risk factor for IHD [13, 14], recent reports have paid particular attention to HDL concentrations [7–9]. The HDL2 subfraction of HDL as opposed to the HDL3 subfraction accounts for much of the variation in serum HDL concentration in the general population, and it is the HDL2 subfraction which is probably most closely associated with IHD risk [15, 16]. Thus far, however, there are no reports of serum HDL subfractions in patients with NS but without severe renal failure. Altered lipoprotein metabolism in NS may be due to a variety of factors [17] including the loss of HDL in the urine [18]. We have studied serum lipid and lipoprotein concentrations, including HDL subfractions, and, as a marker of urinary HDL output, urinary apolipoprotein A1 (apo A1) concentration, in a well characterized group of patients with NS and relatively well preserved creatinine clearance.

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Methods

Patients

Forty-one adult patients (over 16 years of age) with biopsy–proven glomerular disease currently attending the outpatient clinic were studied. Blood was taken after a 12 hr fast and urine collected for 24 hr. Age, sex, height, wt and blood pressure were recorded, and all patients were interviewed regarding their cigarette and alcohol consumption, exercise pattern and current drug therapy. Of these 41 patients, 21 had both proteinuria >3g/24hr and a creatinine clearance > 35ml/min/1.73m^2. None of these 21 had evidence of multisystem disease such as diabetes mellitus or systemic lupus erythematosus, and none had received corticosteroid or cytotoxic therapy within the previous three months. The histopathological diagnoses were: membranous nephropathy in eight, mesangiocapillary glomerulonephritis in four, mesangial proliferative glomerulonephritis in three, focal and segmental glomerulosclerosis in three and one each of crescentic glomerulonephritis, familial nephritis and "steroid–resistant–no–light–microscopic–change NS". Six patients (four male and two female) were taking beta blocking drugs and ten patients were prescribed diuretics (furosemide in eight and athiazide in two). The control groups consisted of 82 males from a local factory and 19 female nurses and laboratory staff. They were all apparently healthy, none had any historical evidence of IHD or were taking drugs known to affect lipoprotein metabolism. A further five of the original 41 patients (three with membranous nephropathy, one focal and segmental glomerulosclerosis and one steroid–resistant–no–light–microscopic–change NS) who conformed to all the above criteria, except that their creatinine clearances were between 15 and 35 mliter/min/1.73m^2, were included in the analysis of the factors determining urinary apo A1 excretion after it had been established that creatinine

Table 1. Characteristics (mean ± SEM) of the 21 patients and 101 controls studied in the analysis of serum lipid and lipoprotein concentrations

		Male patients	Male controls	Female patients	Female controls
Number		14	82	7	19
Age	years	44 ± 4	50 ± 1	34 ± 5	41 ± 4
Quetelet index		27 ± 0.8	25.8 ± 0.4	27.7 ± 1.9*	23.6 ± 0.7
Cigarette smokers	%	29	29	29	37
Alcohol intake**	g/week	31.5;0–524	99;0–810	0;0–136	17;0–117
Duration of proteinuria**	months	43;12–120	—	97;9–171	—
Plasma albumin	g/liter	31.8 ± 1.5	—	31.9 ± 1.7	—
Creatinine clearance	mliter per min per 1.73 m^2	74 ± 9	—	75 ± 15	—
Urine protein***	g/24 hr	9.7;3.2–29	—	6.4;3.6–17	—

Symbols are: * $P = 0.02$; ** median;range; *** geometric mean;range.

clearances of this level had no independent effect on urinary apo A1 output. One patient was excluded from the multiple regression analysis because of insufficient data.

Laboratory methods

Serum lipoproteins were isolated by ultracentrifugation at 100,000 × g (Superspeed 65 and 18 × 6.5ml, Aluminium Rotor, MSE Limited, Crawley, Sussex, U.K.) and tube-slicing (Spinco Tube Slicer, Beckman Instruments, Inc., Palo Alto, California, USA). VLDL was separated as the supernatant after ultracentrifugation of plasma for 24 hr and HDL and HDL3 as infranatants after adjustment of plasma density to 1.063 g/mliter and 1.125 g/mliter respectively, and ultracentrifugation after 48 hours [19, 20]. Cholesterol and triglycerides in serum and lipoproteins were determined enzymatically, (cholesterol reagents from DiaLab Ltd., Macclesfield, Cheshire, U.K. and triglycerides by Peridochrome method, Boehringer Mannheim Corporation Ltd., Lewes, E. Sussex, U.K.). The concentration of HDL2 cholesterol was calculated by subtraction of HDL3 cholesterol concentration from that of total HDL. Serum LDL cholesterol concentration was calculated from serum triglycerides and HDL cholesterol [21]. Serum apolipoprotein B (apo B) and serum and urinary apo A1 were determined by electroimmunoassay [22, 23]. Plasma albumin and creatinine were measured using standard autoanalyzer methods in the service laboratory. Urine protein was measured by a turbidometric method and selectivity index was determined by the ratio of IgG:transferrin clearances [24]. Before determination of both apo A1 and selectivity, urine was first concentrated tenfold by dialysis against polyethylene glycol 6000 across a membrane with a mean pore radius of 24 angstroms (Dialysis Tubing Visking, Medicell International Ltd., London, U.K.). Pre- and post-concentration assays had determined an apo A1 recovery of 84 ± 0.98% (mean ± SEM, N = 10 experiments). Pre- and post-results given in this report are uncorrected for recovery.

Statistical methods

Unpaired *t*-tests (two-tailed) were used to compare two means with the appropriate corrections if the variances were unequal. Log transformations were used for positively skewed variables. Multiple linear regression analyses were carried out according to the Statistical Package for the Social Sciences [25].

Table 2. Serum lipid and lipoprotein concentrations (mean ± SEM) in 14 male patients and 82 healthy men[a]

	Male patients	Male controls
Total serum cholesterol, *mmole/liter*	7.46 ± 0.66	6.40 ± 0.13
Total serum HDL cholesterol, *mmole/liter*	1.35 ± 0.09	1.40 ± 0.04
Serum HDL2 cholesterol, *mmole/liter*	0.54 ± 0.10[c]	0.75 ± 0.04
Serum HDL3 cholesterol, *mmole/liter*	0.81 ± 0.07[d]	0.63 ± 0.02
Serum LDL cholesterol, *mmole/liter*	5.09 ± 0.58	4.33 ± 0.14
Serum VLDL cholesterol,[b] *mmole/liter*	0.94;0.32–2.17[e]	0.45;0.07–4.23
Serum triglycerides,[b] *mmole/liter*	1.78;0.43–4.37	1.31;0.36–3.96
Serum apolipoprotein B, *g/liter*	1.30 ± 0.10	1.14 ± 0.03
Serum apolipoprotein Al, *g/liter*	0.88 ± 0.05[e]	1.08 ± 0.02

[a] Conversion factors; cholesterol: mg/dliter = mmole/liter × 39. triglycerides: mg/dliter = mmole/liter × 89.
[b] geometric mean;range; [c] $P < 0.05$; [d] $P < 0.01$; [e] $P < 0.001$.

Results

Characteristics of patients studied

Age, alcohol and cigarette consumption were not significantly different between patients and controls (Table 1). The female patients were more obese than controls. In the patients, proteinuria was never less than 3.2 g/24hr and had been present for a minimum of nine months. Plasma albumin in men and women was inversely related to the log urinary protein output ($r = -0.72$, $P < 0.001$, $N = 21$).

Serum lipid and lipoprotein concentrations

In male patients serum HDL3 cholesterol concentration was higher and HDL2 lower than in controls (Table 2). Like serum HDL2, the concentration of serum apo A1 was significantly decreased in men with proteinuria. Concentrations of total HDL cholesterol were, however, similar in the two groups of men. Serum VLDL cholesterol was significantly higher in the male patients, whereas serum triglycerides, serum cholesterol, serum LDL cholesterol and serum apo B, although numerically higher in the male patients, were not significantly different from controls. In women, serum LDL cholesterol concentration was increased in patients (Table 3). Otherwise, no statistically significant differences were found. However, there were fewer women than men, and with the exception of HDL3 cholesterol,

Table 3. Serum lipid and lipoprotein concentrations (mean ± SEM) in seven female patients and 19 healthy women

	Female patients	Female controls
Total serum cholesterol, *mmole/liter*	7.22 ± 0.86	5.55 ± 0.22
Total serum HDL cholesterol, *mmole/liter*	1.55 ± 0.24	1.77 ± 0.14
Serum HDL2 cholesterol, *mmole/liter*	0.68 ± 0.18	0.85 ± 0.10
Serum HDL3 cholesterol, *mmole/liter*	0.87 ± 0.20	0.92 ± 0.07
Serum LDL cholesterol, *mmole/liter*	4.97 ± 0.71[b]	3.15 ± 0.21
Serum VLDL cholesterol,[a] *mmole/liter*	0.50;0.13–2.25	—
Serum triglycerides,[a] *mmole/liter*	1.42;0.80–2.40	1.27;0.78–6.03
Serum apolipoprotein B, *g/liter*	1.31 ± 0.21	—
Serum apolipoprotein Al, *g/liter*	0.96 ± 0.10	—

[a] geometric mean;range.
[b] $P < 0.05$.
For conversion factors, see Table 2.

Table 4. Characteristics (mean ± SEM) of the 26 men and women with proteinuria studied in the analysis of urinary apolipoprotein Al excretion

	Male patients	Female patients
Number	17	9
Urinary protein,[b] *g/24 hr*	9.7;3.2–29.0	7.6;3.6–28.5
Total serum HDL cholesterol, *mmole/liter*	1.32 ± 0.08	1.52 ± 0.21[c]
Serum HDL2 cholesterol, *mmole/liter*	0.51 ± 0.09	0.63 ± 0.17[c]
Serum HDL3 cholesterol, *mmole/liter*	0.81 ± 0.06	0.95 ± 0.18
Selectivity index[b]	0.33;0.16–0.80	0.30;0.14–0.50
Urinary apolipoprotein Al,[a] *mg/24 hr*	9.3;0–450.4	32.2;0–193

[a] median;range.
[b] geometric mean;range.
[c] $N = 8$.

the concentrations of which were similar in patients and controls, trends were the same as those in men.

Analysis of factors determining serum HDL subfraction cholesterol concentrations

Our male controls and patients were well matched with respect to variables known to influence serum HDL. However, in order to be sure that the differences in HDL subfractions observed were not due to these other variables, multiple regression analysis was undertaken. In our model, cigarette smoking, alcohol consumption and nephrotic syndrome were included as dummy variables and Quetelet Index (reciprocal), log serum triglycerides and serum LDL cholesterol concentration as continuous variables. In the 96 men (14 patients and 82 controls) included in the analysis, nephrotic syndrome was the only factor contributing significantly to the variation in HDL3 ($P = 0.001$); for the full model multiple $r = 0.40$, $P = 0.015$. There were, however, significant contributions to the variation in serum HDL2 concentration from serum LDL cholesterol concentration ($P = 0.017$) and to the variation in total HDL cholesterol concentration from alcohol intake ($P = 0.012$) and serum LDL cholesterol concentration ($P = 0.015$).

Determinants of urinary apolipoprotein Al

Determinants of urinary apo A1 excretion were studied in 26 patients (creatinine clearances >15ml/min/1.73m^2), details of whom are shown in Table 4. There was no measurable urinary apo A1 (lower limit of detection 0.01 g/liter of concentrated urine) in seven patients. Of these, the selectivity index was less than 0.26 in six, whereas in 17 of 19 patients with detectable urinary apo A1, the index was 0.26 or greater ($P < 0.002$, two-tailed Fisher's exact test). In those in whom urinary apo A1 was detectable, its output was related to both selectivity index (Fig. 1) ($r = 0.66$, $P < 0.005$) and to total urinary protein output ($r = 0.5$, $P < 0.005$). A stepwise multiple linear regression analysis was undertaken which included sex, serum HDL, HDL2 and HDL3 cholesterol, log urinary protein output, log selectivity index and creatinine clearance as variables in the

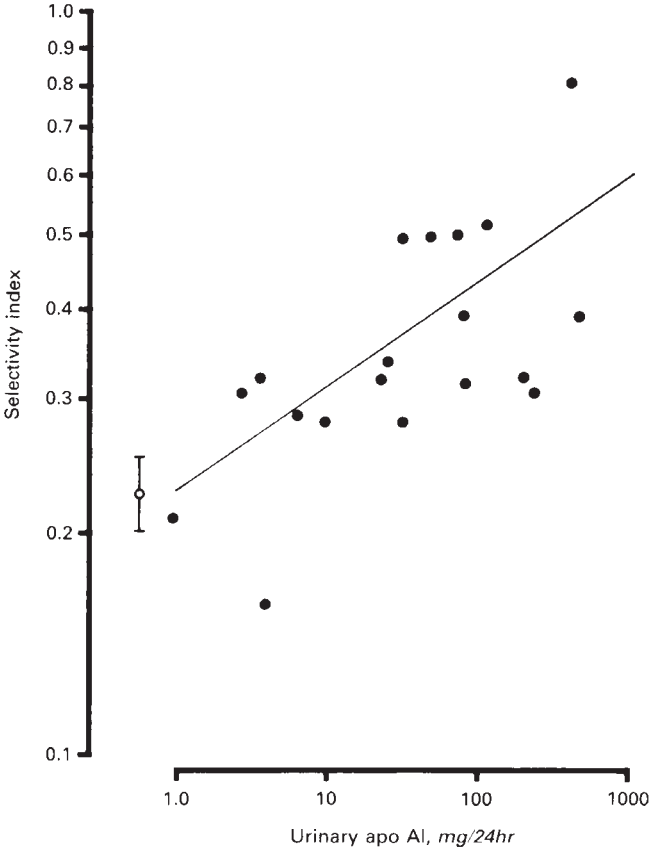

Fig. 1. *Urinary apolipoprotein A1 output as a function of selectivity index in 19 patients with detectable urinary apo A1* (●). $r = 0.66$, $P < 0.001$. Mean (± SEM) selectivity index of seven patients without detectable urinary apo A1 (0).

18 patients with detectable urinary apo A1 in whom data was complete. Only two of these variables made a significant ($P < 0.05$) contribution to the variation of urinary apo A1. These were in order of importance log selectivity index (42% of variation) and log urinary protein (27% of variation). The full multiple regression equation was:

Urinary apo A1 = 3.325 ± 0.690 log selectivity index + 1.481 ± 0.407 log urinary protein output + 1.440 ± 0.513 (multiple $r = 0.83$, $P < 0.001$).

Discussion

Patients with NS frequently have raised serum total LDL cholesterol concentrations (6) but reports concerning serum HDL cholesterol are conflicting; both high and low levels have been found (6–9, 26, 27). This is probably because of considerable differences in other aspects of renal function, treatments and other characteristics known to affect HDL metabolism.

This is the first report of HDL subfraction cholesterol levels in patients with primary, biopsy–proven glomerular disease with nephrotic range proteinuria (>3g/24hr) and well maintained renal function (creatinine clearance >35ml/min/1.73m^2). The patients had well maintained plasma albumin concentrations despite heavy proteinuria. Our experience over many years suggests that with the appropriate protein and calorie supplementation, this can be achieved in most patients who are metabolically stable. Our study demonstrates that raised serum HDL3 and reduced HDL2 cholesterol are found in male patients despite normal total serum HDL cholesterol concentrations. Furthermore, the rise in HDL3 in the proteinuria patients was shown to be largely due to NS rather than to differences between patients and controls in other variables known to influence serum HDL subfractions. A similar trend towards lower serum HDL2 cholesterol concentrations was observed in women. However, we were able to study only a small number of women with NS who were markedly obese. One earlier report, however, describes lowered serum HDL2 cholesterol concentrations, and occasionally raised serum HDL3 cholesterol concentration, but this was in a group consisting mainly of children who had severe renal impairment and relatively modest proteinuria [7].

Lipiduria has long been recognized in NS [28] and it is well established that much of this lipid is in lipoproteins of similar hydrated density to HDL [18, 27, 29, 30]. In our study apo A1, the major component of the protein moiety of HDL, was determined in urine as a measure of the urinary HDL leak. Its output was largely determined by the selectivity of the proteinuria and by the total urinary protein. This conclusion is supported by an earlier report that selectivity was related to the ratio of total urinary apo A to total proteinuria in younger patients with non-minimal change NS [27]. The implication of these findings is that the functional diameter of the abnormal 'leaky pores' in the glomerular basement membrane, and their relative abundance as judged by the degree of proteinuria, determine the quantity of HDL lost into the urine.

It might be anticipated that smaller HDL particles would be lost into the urine in preference to larger ones, and therefore that HDL3 (molecular wt 175,000 daltons and mean diameter of 55 angstroms) might be lost in preference to HDL2 (molecular wt 360,000 daltons and mean diameter 85 angstroms), and nascent HDL would be lost in preference to either of them. In the serum however, HDL3 levels were high and HDL2 levels were low. This apparent paradox may be explicable as follows: in NS there is a general increase in hepatic lipoprotein secretion [31–33] which is probably a consequence of low serum albumin or lowered plasma oncotic pressure [6, 33]. In our patients, indirect evidence for an increased production of HDL comes from the observation that some of our male patients were losing 50 to 100% of the apo A1 normally synthesized in a day [14, 34] directly into their urine. Since their total serum HDL cholesterol concentrations were normal, this indicates that those with the greatest losses must have been able to at least double their rate of apo A1 production. This increase in rate of production of apo A1 presumably reflects increased production of nascent HDL. The loss of HDL particles into urine will reduce their plasma half life [34, 35] so that although nascent HDL may remain in the circulation long enough to acquire sufficient cholesterol to be converted to HDL3, substantial amounts of both nascent HDL and HDL3 will have disappeared into the urine before the larger HDL2 particles can be formed [7]. Such an effect may be compounded by defects in the metabolism of triglyceride rich lipoproteins [26, 31] which is also important for the conversion of HDL3 to HDL2. The result would be an increased HDL3 and a lowered HDL2 as found in this study.

The present findings should be considered in the context of the controversy about the prevalence of IHD in NS [9–12]. High levels of serum LDL and VLDL, both of which occur in NS, are positive risk factors for the development of IHD in the general population [36, 37], but serum HDL appears to be a negative risk factor [13]. The levels of the HDL2 subfraction, which were low in our patients with proteinuria, may be more closely associated with this apparent protection [15, 16] than those of HDL3, the other major subfraction of HDL. The protein moiety of HDL2 is relatively richer in apo A1 than that of HDL3 [14] and this may account for the decreased serum concentration of apo A1 in our patients with proteinuria. Decreased levels of serum apo A1 have recently been shown to be closely associated with coronary atheroma [38]. A tendency for high levels of serum apo B similar to that in the proteinuria patients in our study has also been implicated as an important determinant of coronary atherosclerosis risk [39, 40]. Our findings suggest that lipoprotein risk factors for IHD may vary widely in patients with NS, and that such patients cannot be considered as a homogenous group in this respect, a case we have previously argued [11]. Patients with highly selective proteinura (such as, minimal change nephropathy) or, more specifically, a selectivity index of less than 0.26 and/or relatively small degrees of proteinuria may lose very little HDL into their urine. However, patients with heavy, poorly selective proteinuria will lose a substantial amount of HDL into their urine. This will account for a large proportion of the daily turnover of HDL and be responsible, at least in part, for abnormal levels of HDL subfractions, as reported here, and lead to accelerated atherogenesis.

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